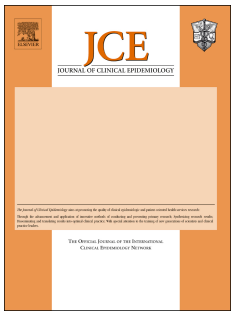

Methodology and Design of Platform Trials: A meta-epidemiological study

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Abstract

Introduction:

Adaptive platforms allow for the evaluation of multiple interventions at a lower cost and have been growing in popularity, especially during the COVID-19 pandemic. The objective of this review is to summarize published platform trials, examine specific methodological design features amongst these studies and hopefully aid readers in the evaluation and interpretation of platform trial results.

Methods:

We performed a systematic review of EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and clinicaltrials.gov from January 2015 to January 2022 for protocols or results of platform trials. Pairs of reviewers, working independently and in duplicate, collected data on trial characteristics of trial registrations, protocols, and publications of platform trials. We reported our results using total numbers and percentages, as well as medians with interquartile range (IQR) when appropriate.

Results:

We identified 15,277 unique search records and screened 14,403 titles and abstracts after duplicates were removed. We identified 98 unique randomized platform trials. Sixteen platform trials were sourced from a systematic review completed in 2019, which included platform trials reported prior to 2015. Most platform trials (n=67, 68.3%) were registered between 2020-2022, coinciding with the COVID-19 pandemic. The included platform trials primarily recruited or plan to recruit patients from North America or Europe, with most subjects being recruited from the United States (n=39, 39.7%) and the United Kingdom (n=31, 31.6%). Bayesian methods were used in 28.6% (n = 28) of platform RCTs and frequentist methods in 66.3% (n = 65) of trials including 1 (1%) that used methods from both paradigms. Out of the twenty-five trials with peer reviewed publication of results, seven trials used Bayesian methods (28%) and of those, two (8%) used a pre-defined sample size calculation while the remainder used pre-specified probabilities of futility, harm, or benefit calculated at (pre-specified) intervals to inform decisions about stopping interventions or the entire trial. Seventeen (68%) peer reviewed publications used frequentist methods. Out of the seven published Bayesian trials, seven (100%) reported thresholds for benefit. The threshold for benefit ranged from 80% to >99%.

Conclusion:

We identified and summarized key components of platform trials, including the basics of the methodological and statistical considerations. Ultimately, improving standardization and reporting in platform trials require an understanding of the current landscape. We provide the most updated and rigorous review of platform trials to date.

Introduction

Adaptive platform trials allow for the simultaneous comparison of multiple interventions examining a specific clinical condition, often employing a common control or comparator arm. Platforms employ statistical rules (ideally pre-specified but not always) that inform the threshold and timing of conclusions for each intervention of interest. New interventions can also be added, even after the trial has been initiated (1-6). Due to the efficiency in evaluating multiple treatments across shared trial infrastructure, platform trials facilitate clinical trial conduct, maximizing recruitment efficiency across interventions. This framework can potentially allow for the evaluation of multiple interventions at a lower cost (7).

Adaptive platform trials have been used in fields such as oncology and infectious diseases, however the COVID-19 pandemic demonstrated the true value of these trials by allowing rapid and simultaneous assessment of multiple potential therapeutics options for this novel disease. For example, Randomised Evaluation of COVID-19 Therapy (RECOVERY), Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP), Repurposed Approved and Under Development Therapies for Patients With Early-Onset COVID-19 and Mild Symptoms (TOGETHER) and the Platform randomised trial of interventions against COVID-19 In older people (PRINCIPLE) platform trials have provided key evidence informing clinical practice establishing the benefit of corticosteroids, IL-6 receptor blockers, and JAK2 inhibitors for the treatment of patients with COVID-19 and have informed international clinical practice guidelines (8-11).

Because of the innovative design features employed in these trials, adaptive platform trials introduce a number of challenges for trial design, analysis, and interpretation. Stopping or decision rules must be carefully pre-specified, and there remain issues in evaluating the rigour and appropriateness of these key platform design decisions. Recently, CONSORT guidelines have been published in an effort to standardize reporting, but challenges remain (12). For traditional randomized controlled trials (RCTs), stopping the trial early based on interim data analysis is generally considered to be a possible source of bias, whereas in an adaptive platform trial, routine adaptive analysis and application of dynamic stopping decisions is inherent to the trial design. Use of non-concurrent controls or comparator patients can also contribute to baseline imbalance between study arms, which may result in bias. These challenges are compounded by the fact that many clinicians, clinical trialists and evidence stakeholders are still early in their understanding of platform trial methodology.

We present a meta-epidemiological study reporting the characteristics, design, and methodological decisions of published platform trials. The objective of this review is to summarize published platform trials, examine specific methodological design features amongst these studies and hopefully aid readers in the evaluation and interpretation of platform trial results.

Methods

We registered a protocol on Open Science Framework (https://osf.io/9su86) on January 27th 2022. We report results according to PRISMA reporting guidelines (13, 14).

Search strategy

Along with an experienced research librarian, we designed a comprehensive search strategy. We based the initial search strategy on a recent systematic review, combining key words and subject headings for "adaptive trial", "master protocol", "multi-arm trial" or "platform trial" (15). We searched EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and clinicaltrials.gov from January 2015 to January 2022 for protocols or results of platform trials. We chose to start the search in 2015 given most platform trials have been published in the last 7 years, and as a pragmatic decision to manage resources required for the review.

We supplemented the search by reviewing the citations of previous reviews of adaptive and platform trials (3, 5, 7, 15). eTable 1 presents the full search strategy.

Study eligibility

We included peer-reviewed publications, pre-prints, abstracts, and technical documents that were publicly accessible or retrieved through contact with trial investigators and described either platform trial protocols or results from platform trials.

For the purpose of this review, we defined platform trials as randomized controlled trials (RCTs) that evaluate several interventions simultaneously within a single protocol targeted at a specific disease or syndrome, with the flexibility to drop and add new interventions during the trial (1, 16). Although there is inconsistency in how platform trials have been defined, this definition is based on recent educational and guidance publications addressing platform trials (3-6) .

We did not exclude trials based on language of publication, disease, patient population or type of treatment investigated. We included multiple documents for each included trial such as publication of results, protocols and trial registrations.

Study selection

Following training and calibration exercises to ensure sufficient agreement, pairs of reviewers, working independently and in duplicate, screened titles and abstracts of search records. For any citation deemed potentially relevant by either reviewer, we reviewed the full texts again independently and in duplicate, before deciding on final eligibility. At the full text stage, we resolved discrepancies by discussion, or, if necessary, by third party adjudication.

When trial registrations or publications were identified without a publicly available protocol, we contacted investigators asking them to share their protocol.

Data collection

Pairs of reviewers, following training and calibration exercises to ensure sufficient agreement, extracted data independently and in duplicate. Reviewers resolved discrepancies and disagreements by discussion or by third party adjudication when necessary.

When we identified a manuscript, we attempted to identify the corresponding protocol. We extracted data from both platform trial protocols and manuscripts describing the results of platform trials. For trials with multiple versions of the same protocol, we collected data from the most recent publicly available version. For platform trials without publicly accessible protocols, or for those that did not respond to requests for sharing protocols, we collected data from trial registrations.

We collected data on trial characteristics (e.g. trial registration number, date of publication, disease area of study, number randomized, interventions, and comparators), general trial methods (e.g. blinding, allocation concealment, governance structure), and statistical methods (e.g. Bayesian vs. frequentist). eTable 2 presents the data collection form.

Data synthesis

We present results narratively using tables or graphs when applicable. We report medians and interquartile range (IQR) for continuous outcomes and proportion and percentages for categorical outcomes.

We report the results in total number of platform trials reporting a specified outcome. For each item, the denominator is the same (i.e., 98).

Results

Search

We retrieved 15,277 unique search records and screened 14,403 titles and abstracts after duplicates were removed. We screened 453 records in full-text and identified 105 unique platform trials. Sixteen platform trials were sourced from a systematic review completed in 2019, which included platform trials reported prior to 2015. Of the 105, we identified seven trials that were described as platform trials but were not randomized studies and were therefore excluded (17-23). For the remaining 98 trials, there were 31 (31.6%) trials with a publicly accessible protocols of which 23 were peer reviewed; 25 (25.5%) platform trials with peer-reviewed publications of results and 42 (41%) with only trial registration data available (e.g. national clinical trial registry, no protocol) (22-122).

Figure 1 presents the selection of search records and eTable 3 presents a list of the included platform trials with associated summary of findings for published articles.

Timeline of trials and trial status

The first platform trial included was from 2004 (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE)), with an increasing number of publications and registrations after 2019. Most platform trials (n=67, 68.3%) were registered between 2020-2022, coinciding with the COVID-19 pandemic. At the time of data collection, 11 registered platforms were not yet recruiting subjects (13%), 71 were actively recruiting (71%), and 16 (16%) were completed or terminated.

Figure 2 presents details on the timeline of the emergence of platform trials.

Financial support and public involvement

Platform trials were funded by variety of sources, often reporting multiple sources simultaneously, including government (n=45, 46%)), institutions (e.g., universities) (n=38, 38.7%), industry (n=31, 31.6%) and not-for-profits (n=28, 28.5%).

Only eight trials (8.2%) reported involving the public and patients in the design of the trial but most often, no mention of public involvement was reported.

Characteristics of Trials

The included platform trials primarily recruited or plan to recruit patients from North America or Europe, with most subjects being recruited from the United States (n=39, 39.7%) and the United Kingdom (n=31, 31.6%).

The included platform trials studied or plan to study a wide range of disease states.Infectious diseases were the most common type of disease examined (n=45, 45.9%) of which COVID-19 accounted for most trials (n=37, 37.7%).

Pharmacologic therapies were the most common intervention studied (n=86, 87.7%) and supportive therapies were least common type of intervention (n=4, 4.1%). The most common primary outcome included all-cause mortality (n=24, 24.4%) and outcomes related to long-term morbidity (n=56, 57.1%).

Platform trials often reported an open label design (n=71, 72.4%), rather than blinding patients and investigators to interventions.

Box 1: Blinding procedures in platform trials

Blinding
Most platform trials reported an open label (non-blinded) design, which is often considered a potential compromise of the equalization of prognostic factors achieved through randomization. There has been conflicting evidence on whether lack of blinding actually increases the risk of bias (123). However, a recent methodological study published suggested that the results of critical care trials may be negatively affected by the lack of blinding (124).

Open label designs have the benefit of being less resource intensive and easier to implement. This is especially true in multi-intervention platform trials given the need for multiple placebos. Therefore, when appraising platform trials, one should carefully consider the impact of lack of blinding on risk of bias due to concerns for deviations of the intended intervention, especially in critical care trials.

Examples of platform trials with open label designs:
Durvalumab Alone or in Combination With Novel Agents in Subjects With NSCLC (COAST)(42)
Early Treatment of Vulnerable Individuals With Non-Severe SARS-CoV-2 Infection (COVERAGE-A) (45)

Examples of platform trials with double-blind designs:
Better Evidence and Translation for Calciphylaxis (BEAT-Calci) (40)
MS-SMART: Multiple Sclerosis-Secondary Progressive Multi-Arm Randomisation Trial (MS-SMART) (71)

Table 1 presents more detail on the trial characteristics.

Statistical methods

Bayesian methods were used in 28.5% (n = 28) of platform RCTs, frequentist methods in 66.1% (n = 65), and 1 (1%) used methods from both paradigms.

The criteria for adding new interventions were not clearly reported in most platform trials. When this information was reported, there were many factors considered when deciding to add new interventions onto the platforms. These included the emergence of external evidence supporting the new intervention (n=30, 30.6%), reduced cost potential (n=3, 3.1%), promising safety profile (n=5, 5.1%), and biologic plausibility or physiologic data (n=6, 6.1%). Most trials used clinical research evidence of potential efficacy of an intervention as the primary method of determining whether to add an intervention to the study, whereas costs was the least common deciding factor.

Thirty-six trials (36.7%) reported more than one primary outcome and the median number of interventions investigated across each platform trial was 5 (IQR 3-6).

Box 2: New interventions in platform trials

New interventions
One of the strongest advantages of adaptive platform trials is the ability to drop interventions based on a set of pre-established criteria. This allows for rapid and efficient clinical assessment of potential interventions.

For example, the **I-SPY platform trial (Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer)** started recruiting in 2010. It has consistently published data on drug treatments for breast cancer, with 28 active interventions tested. A more recent example is RECOVERY, a large platform trial that been able to add and drop interventions throughout the COVID-19 pandemic, providing high quality evidence for clinicians (11).

Most trials (n=58, 59.1%) reported using or planning to use a fixed randomization ratio, but a substantial proportion employed response-adaptive randomization (n=31, 31.6%). Seven trials (7.1%) reported using or planning to use co-variate adaptive (minimization) methods for randomization and one used both adaptive and mixed randomization. Of the twenty-five platform trials with publications, seventeen (68%) used simple randomization, seven (28%) used response adaptive, and one used minimization methods (4%)

Box 3: Methods of randomization

Fixed randomization
Fixed randomization refers to allocation of interventions or comparator based on a single sequence of random assignments (125). For example, the **Platform Study of Belantamab Mafodotin as Monotherapy and in Combination With Anti-cancer Treatments in Participants With Relapsed/Refractory Multiple Myeloma (DREAMM-5)** trial uses a simple randomization method with a 1:1 ratio (126).

Co-variate adaptive (minimization)
Co-variate adaptive methods for randomization assess for imbalances of sample size among several covariates (125). **Evaluation of SQ109, High-dose Rifampicin, and Moxifloxacin in Adults with Smear-positive Pulmonary TB in a MAMS Design (PanACEA) trial** randomized participants using a probabilistic minimisation algorithm based on site, baseline TB bacterial load and HIV status (127).

Response-Adaptive
Adaptive randomization refers to protocols that allow adjustment of the probability of treatment assignment according to pre-specified variables or conditions. **Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP)** used an adaptive randomization method. In REMAP-CAP, random allocation occurred with a weighted probability for each intervention, with the weighted probability being proportional to the extent to which similar participants recruited earlier in the trial benefited or not from each intervention. Therefore, the randomization ratio is dynamic and changes as the trial changes.

In all included platform trials, Bayesian trials most often did not use or report a pre-defined sample size but instead, used or planned to use pre-specified probabilities of futility, harm, or benefit calculated at (pre-specified) intervals to inform decisions about stopping interventions. Eleven Bayesian trials (39.2%)

reported using or planning simulations to inform sample size calculations. Frequentist trials most used pre-determined sample sizes (n=54, 83.1%) and fewer used simulations to inform sample sizes as compared to Bayesian trials (n=6, 9.2%).

Out of the twenty-five (over 70 individual publications) trials with peer reviewed publication of results, seven trials used Bayesian methods () and of those, two (28.5%) used a pre-defined sample size calculation while the remainder used pre-specified probabilities of futility, harm, or benefit calculated at (pre-specified) intervals to inform decisions about stopping interventions or the entire trial. Six (86%) used simulations to inform sample size calculations. Seventeen (68%) peer reviewed publications used frequentist methods and fifteen (88.2) calculated a pre-specified sample size.

Out of the seven published Bayesian trials, seven (100%) reported thresholds for benefit. The threshold for benefit ranged from 80% to >99%.

Table 2 presents more detail on the statistical methods and eTable 3 on the summary of findings of the individual platform trials.

Discussion

Main findings

The use of platform trials has increased in the past few years, from a relatively uncommon method of conducting an RCT to a rapidly applied design methodology with wide reaching impact in the COVID-19 pandemic and beyond. Prior to 2020, there were only 16 platform trials, and although most platform trials after 2020 were COVID-19 related, we saw a diversification of the types of disease processes examined. For example, chronic neurodegenerative disorders such as ALS (HEALEY ALS Platform Trial) and Multiple Sclerosis (MS-SMART: Multiple Sclerosis-Secondary Progressive Multi-Arm Randomisation Trial) have specific platform trials, which did not exist before, allowing for more efficacious and rapid assessment of potentially practicing changing interventions. Platforms have also been used to address such diverse clinical conditions as identifying strategies for increasing HIV testing in vulnerable populations and reducing depressive relapses.

We found that most platform trials investigate pharmacologic therapies, are open label, use Bayesian analysis and fixed methods for randomization. We found that most trials had more than 2 arms and reported external clinical evidence as the most common reason for adding an intervention.

Most platform trials recruited or plan to recruit subjects disproportionally from high income countries, with the majority from North America and Europe.

In relation to previous findings

A systematic review and meta-analysis of adaptive trials conducted in 2019 identified 16 platform trials (15). They noted an increase in the uptake of adaptive trials overall. As we have noted, prior to 2020,

adaptive trials (including platform trials) most often investigated oncological diseases rather than other disease processes. Our review shows an important increase in the number of platform trials since the publication of this previous review, with much more diversity in interventions and disease processes. Furthermore, we provide more details on the trial structure and statistical methods commonly used in platform trials.

We also provide educational guidance for those unfamiliar with platform trials, a crucial component of our review, as we believe that the trend of platform trials is only increasing and will likely cover more disease areas in the next few years. For context, there were more platform trials in 2021-22 than all the years prior to this.

Novel findings and impact

This review provides clinicians, trialists, and evidence stakeholders an overview of platform trials. Many clinicians and evidence stakeholders are still not acquainted with key terminology ('Bayesian', 'decision rules', 'responsive adaptive randomization') and common design structures that may influence risk of bias assessments (e.g., open label design). It is well known that platform trials are more efficient and can produce practice-changing trials in rapid fashion. We demonstrate that platform trials are becoming more common outside of their traditional areas (e.g., oncology) and that these types of trials can be employed in essentially any disease area, potentially encouraging trialists to explore this trial design. Incomplete knowledge of platform trials can result in poorly designed trials in the future. Therefore, we provide trialists interested in platform trials with an overview of their structure and design. Our review provides a comprehensive list of platform trials, both successful and unsuccessful, which can help guide future designs and research in the hopes of optimizing methods and reporting.

Strengths and Limitations

Our review has notable strengths and limitations. We performed a careful systematic review of the evidence base, screening an extensive citation list of over 15,000 records to identify a comprehensive list of platform trials. We included not only publications, but protocols and trial registrations, reducing the risk of omission.

A notable limitation includes the search strategy and sensitivity of the search, as there are multiple definitions of platform trials and often, the name 'platform trial' and 'multi-arm, multi-stage' is not listed in the title or abstract. Although we did our best to generate an overly sensitive search, it is possible we have missed eligible platform trials. Furthermore, our search strategy captures platform trials up to January 2022 and the number of existing platform trials likely has increased since then. The trends and methodological patterns, however, are likely to be similar.

Another limitation is the heterogenous data sources we collected from. Namely, out of the 98 trials included, only 25 had peer reviewed publication of results. Therefore, there is potential we are over or under estimating aspects of platform trials. However, in areas where this might be misleading (i.e. in

statistical methods), we report these separately. Another limitation is that the quantitative synthesis was not able to capture important aspects of the platform trial process including the nature and manner of collaboration across institutions, strategies for presenting novel designs and consent paradigms to research ethics boards, or approaches to securing funding for perpetual as opposed to finite trials.

Conclusions

We have identified 98 platform trials, an important increase from 2020, examining a growing number of disease areas. We identified and summarized key components of platform trials, including the basics of the methodological and statistical considerations. We introduce the key concepts of platform trials for evidence users and clinicians. Ultimately, improving standardization and reporting in platform trials require an understanding of the current landscape. We provide the most updated and rigorous review of platform trials to date.

Declarations

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Conflicts of interests/competing interests: None

Contributions: TP, DZ and BR conceived the study idea. SC, EC, NK, GL, RV, and JM helped collect screen and collect data. CY, EG, SM, AH and BR provided content expertise. BR and DZ contributed equally to supervising the study. TP is the data guarantor.

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664 **Table 1. Platform trial characteristics***

Characteristics	n (%)
Number of individual platform trials	98 (100%)
Trials with available protocols	31 (31.6%)
Trials with publications	25 (25.3%)
Trial registration details only	42 (41.2%)
Type of analysis	
Frequentist	65 (66.1%)
Bayesian	28 (28.5%)
Both	1 (1%)
Not reported/unclear	4 (4%)
Funding sources	
Industry	31 (31.6%)
Government	45 (46.7%)
Institutional	38 (38.7%)
Not-for-profit	28 (28.5%)
Disease area	
COVID19	37 (37.7%)
Solid organ cancer	27 (27.5%)
Primary care	6 (6.1%)
Non-solid cancer	5 (5.1%)
Bacterial infections	5 (5.1%)
Degenerative neurological disease/stroke	5 (5.1%)
Pneumonia	3 (3.1%)
Influenza/other viral	3 (3.1%)

Surgical	3 (3.1%)
Pediatric	2 (2%)
other	2 (2%)
Types of interventions**	
Pharmacologic	86 (87.7%)
Surgical	3 (3.1%)
Supportive	4 (4.1%)
Other	8 (8.2%)
Primary outcome	26 (26.5%)
Mortality	56 (57.1%)
Morbidity	8 (8.2%)
Service related	3 (3.1%)
Surrogate outcomes	33 (33.6%)

*Numbers that do not add up to 98 are missing and numbers that exceed 98 indicate trials reporting one or more options.

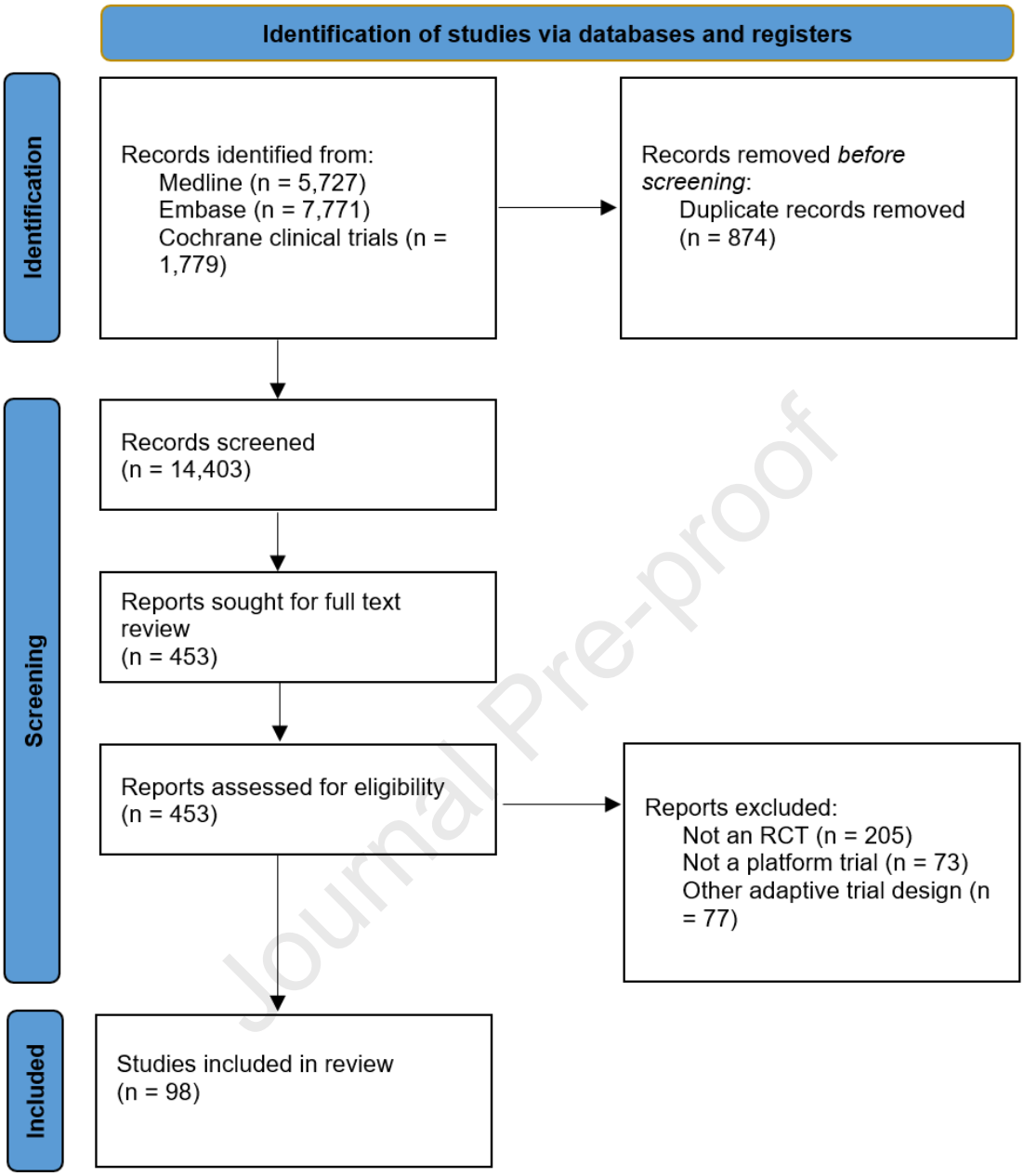
677

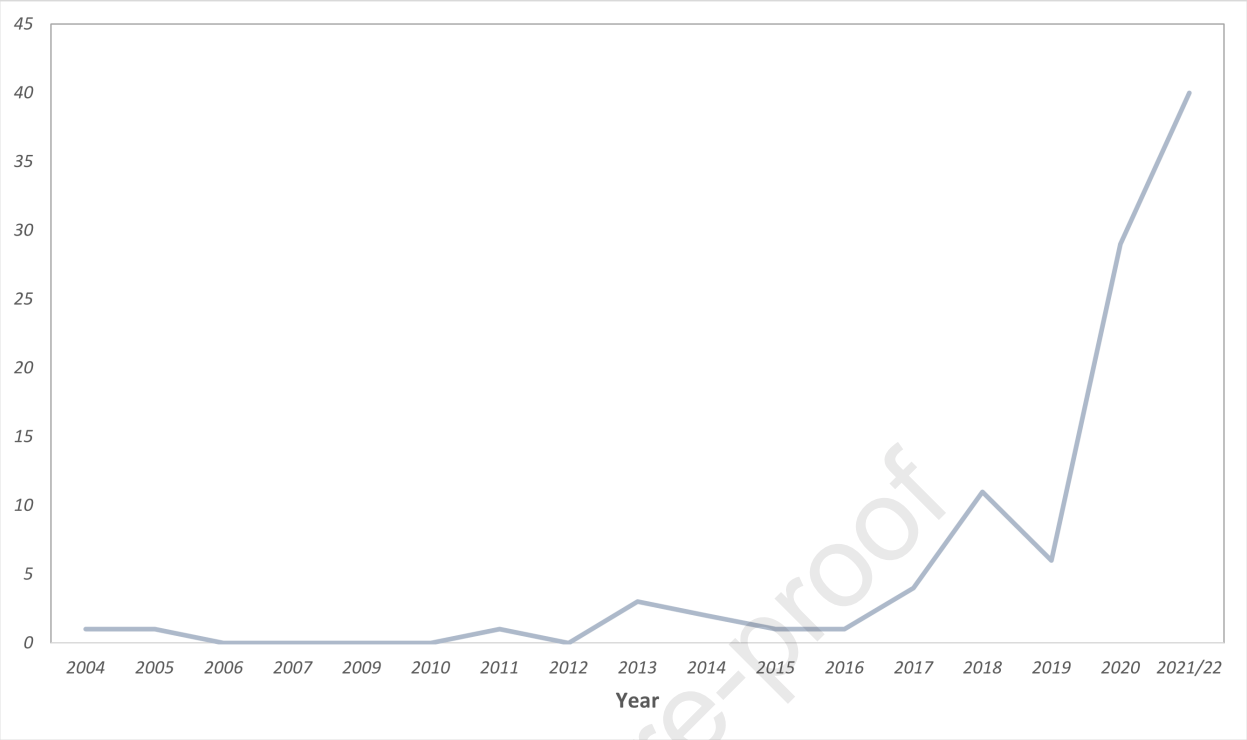
678 **Table 2. Trial structure and statistical methods***

Randomization method	n (%)
Simple	58 (59.1%)
Minimization	7 (7.1%)
Adaptive	31 (31.2%)
Blinding	
Open label	71 (72.4%)
Double blinded	23 (23.4%)
Criteria for adding new interventions	
Biological hypothesis	6 (6.1%)
Clinical research evidence of potential efficacy	30 (30.6%)
Safety profile	5 (5.1%)
Costs	3 (3.1%)
Availability	4 (4.1%)
Trial structure (median (IQR))	
Median number of arms	5 (3 to 6)
Median number of primary outcomes	1 (1 to 3)
Sample size	
Pre-determined	69 (70.4%)
Based on results	15 (15.3%)
Sample size simulations	

Based on simulations	19 (19.4%)
Interim results	
Time	17 (17.3%)
Results	32 (32.6%)

*Numbers that do not add up to 98 are missing and numbers that exceed 98 indicate trials reporting one or more options.





Highlights

- We found a rapid increase in platform trials since the last review, coinciding with the COVID-19 pandemic.
- Platform trials have now been utilised in more diverse areas of medicine, whereas it was previously dominated by oncology and infectious diseases.
- We provide the most updated review of platform trials to-date, including methodological aspects of platform trials and also provide readers with an introduction to platform trials by the way of examples throughout the paper.
- As platform trials become more prevalent, this review can help clinicians and researchers understand platform trials and compare the different approaches taken by successful and unsuccessful models.

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Contributions: TP, DZ and BR conceived the study idea. SC, EC, NK, GL, RV, and JM helped collect screen and collect data. CY, EG, SM, AH and BR provided content expertise. BR and DZ contributed equally to supervising the study. TP is the data guarantor.